REMARKS

Claims 1-12 (as amended) and new claims 13-20 are pending. Support for the claims as amended and the new claims is found in the specification originally filed.

Amendments to claims 1-9 are introduced to recite proper antecedent basis in each of the claims. These claims have not been amended to overcome the art rejections of record.

Claims 13-20 are directed to certain aspects of the claimed invention. Support for the various chloride content ranges is found in the specification originally filed. For example, for the chloride content of 100 ppm or less, Applicant directs the Examiner to page 8, line 26 reciting:

1. Chloride content NMT [no more than] 100 ppm

and to Examples 1 – 10 appearing at pages 17-23 with the Gabapentin (formed according to the claimed invention) having the chloride (ppm) and Gabalactam content (%) as noted in Summary Table 1 below:

Summary Table 1		
Example No.	**Chloride Content of formed Gabapentin (ppm)**	**Gabalactam Content of formed Gabapentin (%)**
1	40	0.01
2	50	0.03
3	60	0.02
4	90	0.04
5	50	0.04
6	60	0.04~~5~~
7	70	0.04<u>5</u>
8	90	0.04
9	90	0.045
10	95	0.04

Thus, in view of the foregoing Summary Table 1, support for the ranges recited in claims 13-20 is found in the specification originally filed including its Examples. Also, support for the process

of claims 19-20 excluding ion exchange conversion of gabapentin hydrochloride is found in the specification originally filed at page 10, lines 4-7 stating in relevant part:

> Another objective of the present invention is to provide an improved process for the preparation of gabapentin, which does not involve the costly ion exchange conversion of gabapentin hydrochloride, making the process simple and economical. [(Emphasis added.)]

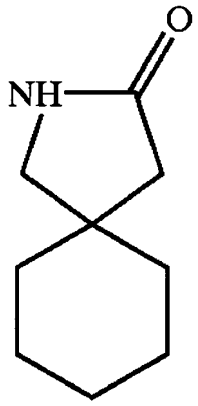
With respect to amended claims 10-12, base claim 10 has been re-written in independent form and the claims further amended for improved clarity.

In view of the foregoing, no new matter (35 USC § 132) has been introduced by the clarifying amendments to claims 1-12 and by the introduction of claims 13-20.

Claim Objections

Claims 7 and 10-12 are objected to for the reasons noted at page 2 of the Office Action. In particular, the "preferably 5.15 C deg" language is objected to as being unclear. Further, claims 10-12 are object to for not expressly reciting "formula 3" of Gabalactam.

To expedite prosecution, Applicant has amended claim 7 to delete the assertedly offending language as noted in the **Listing of the Claims** section of this paper. Also, Applicant has amended claim 10 (and thereby claims 11-12 depending therefrom by virtue of their claim dependency) to expressly recite "formula 3" of Gabalactam which is represented by:



as indicated in the **Listing of the Claims** section of this paper. Accordingly, Applicant respectfully submits that claims 7 and 10-12 (as amended) overcome the objections of record.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the objections of record as they apply to claims 7 and 10-12 (as amended).

Claim Rejections Under 35 USC § 103(a)

Claims 1-9 are rejected as being obvious under 35 USC § 103(a) over the disclosure of U.S. Pat. No. 6,518,456 to Peverali et al. (hereinafter "Peverali") in view of U.S. Pat. Pub. No. U.S. 2004/0068011 to Cannata et al. (hereinafter "Cannata") for the reasons noted at pages 3-5 of the Office Action. Applicant respectfully traverses this rejection for the reasons noted below.

In particular, the Office Action asserts (from page 3, line 12 to page 4, line 4) that:

> **[(1)]** Peverali et al. teaches a process for the preparation of gabapentin by preparing an aqueous solution of gabapentin hydrochloride in water in the ratio of one part by weight of gabapentin hydrochloride to 2.3 part by weight of water (column 5, lines 30-32, example 6). [(Office Action at page 3, lines 12-15; emphasis added.)]
>
> * * *
>
> **[(2)]** Peverali et al. is deficient in the sense that it does not teach recrystalization of precipitate from a mixture of isopropyl alcohol, methanol and water. [(Office Action at page 4, lines 1-2; emphasis added.)]
>
> **[(3)]** Cannata et al., teaches the purification and recrystalization of gabapentin with isopropyl alcohol, methanol and water (page 2, section 28). [(Office Action at page 4, lines 3-4; emphasis added.)]

Unfortunately, each of the foregoing statements identified as **[(1)]**, **[(2)]** and **[(3)]** is inaccurate or a mis-understanding, which forms the basis of the obviousness rejection. Applicant addresses each inaccuracy in order below.

With respect to the first statement in the Office Action marked as **[(1)]** above, a careful reading of Example 6 of Peverali reveals that Peverali is not "preparing an aqueous solution of gabapentin hydrochloride in water" at the ratios noted in the Office Action. In fact, Example 6 of Peverali states, in relevant part, that "gabapentin hydrochloride hemihydrate" (which is not the "gabapentin hydrochloride") is placed in a reactor/reaction vessel:

> EXAMPLE 6
>
> Crude gabapentin
>
> Gabapentin hydrochloride hemihydrate 13.0 kg (59.836 mols) (Analysis--HPLC 99.75%; 0.24% ("lactam"); chemical titre HClO4: 95.6%; KF: 4.4%) and water (30.6 kg) are placed in a 100 l reactor. [(Peverali at col. 5, lines 27-33; emphasis added.)]

Peverali distinguishes its "Gabapentin hydrochloride" from its "Gabapentin hydrochloride hemihydrate" as not being one and the same as noted below. In agreement with that distinction, Peverali finds it necessary to convert "Gabapentin hydrochloride" into "Gabapentin hydrochloride hemihydrate" by digestion with acetone before utilizing the latter hemihydrate in the process of Peverali Example 6:

> The process of the [Peverali] invention comprises the following steps:
>
> 1. Gabapentin hydrochloride is obtained . . . .
>
> * * *
>
> 2. Crude gabapentin hydrochloride is digested in acetone to remove hydrochloric acid, while further reducing the amount of 'lactam' still present. The hemihydrate hydrochloride is obtained after drying.
>
> [(Peverali at col. 2, lines 15-29; emphasis added.)]

From the foregoing, it is clear that the "gabapentin hydrochloride" and the "gabapentin hydrochloride hemihydrate" are certainly not one and the same. If they (the "gabapentin hydrochloride" and the "hemihydrate") were one and the same, there would be no need to form the "hemihydrate" in the first place as taught by Peverali.

In view of the foregoing, the assertion in above-identified statement **[(2)]** that only deficiency of Peverali is that Peverali discloses a different solvent system is incorrect because the "hemihydrate" of gabapentin is not the same as the "gabapentin hydrochloride". Accordingly, Peverali is deficient in at least two respects. This is highly relevant because Applicant's rejected claims recite "gabapentin hydrochloride" and not the "hemihydrate" (of Peverali) as forming an erroneous basis for the obviousness rejection asserted. Thus, Peverali is not only deficient as to failing to disclose, teach or suggest recrystallization from isopropanol (IPA), methanol and water as recited in Applicant's rejected claims, but Peverali is also deficient in failing to disclose, teach or suggest step (i) of Applicant's rejected claims reciting "preparing an aqueous solution of Gabapentin hydrochloride in water in a ratio of one part by weight of the Gabapentin hydrochloride to 0.5 to 3 parts by weight of the water;" as noted in the **Listing of the Claims** section of this paper. (Emphasis added.)

Moreover, as noted, Peverali relies on digestion with acetone to reduce the lactam content. A surprising and unexpected benefit of Applicant's process is that such pre-digestion step to convert the "gabalactam hydrochloride" to a "hemihydrate" and also to reduce the

"lactam" content in the final "gabalactam" so formed (according to Peverali) is not necessary according to Applicant's claimed process – to form Applicant's the resultant gabapentin hydrochloride with low chloride content (e.g., 100 ppm or less) and/or low "lactam" content. See, for example, Summary Table 1 above and also see new claims 13-20 reciting low chloride content and/or low "lactam" content.

Next, with respect to the above-identified statement **[(3)]** in the Office Action asserting that Cannata discloses using an isopropanol (IPA), methanol and water solvent system for re-crystallization of Gabalactam hydrochloride, Applicant respectfully directs the Examiner's attention to cited paragraph [0028] of Cannata reproduced below (in relevant part):

> [0028] Methanol (95 Kg) was added to the residue in four portions and the mixture was heated with water thermoregulated in jacket at 55-60°C for about 1 hour. Isopropylic alcohol (395 Kg) was added to the obtained homogeneous suspension in about 20/30 minutes, with circulation of water thermoregulated at 60-65°C. At the end of the addition, the mixture was kept under stirring for about 30/60 minutes, always with circulating water thermoregulated at about internal temperature 55°C, and then it was cooled first with water and then with saline solution at internal temperature about -5°C. After keeping at this temperature for at least 1 hour, centrifugating and washing with isopropyl alcohol, about 130-140 Kg of wet product were obtained which were dried under vacuum at 50-55°C for about 24 hours obtaining about 120-130 Kg of gabapentin. [(Cannata at page 2, paragraph 0028; emphasis added.)]

From the foregoing text, it is clear that Cannata utilizes methanol and isopropyl alcohol. However, more importantly, the water and the brine (i.e., salt water used at -5°C to prevent its freezing) are used in the "thermoregulated jacket" surrounding the suspension vessel. At no time does paragraph [0028] of Cannata ever disclose, teach or suggest (as erroneously asserted in the Office Action's statement identified and marked as **[(3)]** above) that the water/brine is used for any purpose other than to control the temperature via an external "thermoregulated jacket". (Emphasis added.)

In other words, in direct contradiction to the assertion of above-identified statement [(3)] of the Office Action, Cannata does not disclose, teach or suggest a solvent system of IPA, methanol and water as recited in Applicant's rejected claims.

Moreover, Applicant's claimed invention is able to achieve a low chloride content (e.g., of 100 ppm or less) and/or a low lactam content (e.g., of about 0.045 or less) without the need to first digest (the "gabapentin hydrochloride) in acetone to form a "hemihydrate". Such pre-

digestion step is unnecessary to Applicant's claimed invention in order to achieve the low chloride and/or low lactam content as recited in the rejected claims (as amended).

With that said, with a quite different process using a pre-digestion formed "hemihydrate", Example 6 of Peverali achieves a chloride content corresponding to 0.06% NaCl which is about 364 ppm chloride content – well above 100 ppm or less achieved by Applicant.[1] Furthermore, in that regard, Peverali explains that a NaCl content of 0.02% (or 120 ppm) chloride content can be obtained by his process:

> DETAILED DISCLOSURE OF THE PROCESS
>
> The process of the invention comprises the following steps.
>
> * * *
>
> 5. Crystallization from water is not always necessary, in that sodium chloride concentration can be brought below 0.02% (corresponding to Cl ion $\leq$0.01%) by hot digestion in an ethanol/isopropyl ether or methanol/isopropyl ether mixture. The mixture is then cooled, filtered and dried to obtain almost quantitatively highly pure, anhydrous gabapentin having low content in inorganic salts. [(Peverali at col. 2, lines ~~140~~-~~457~~; emphasis added.)]

which is also unacceptably high above the 100 ppm or less chloride content (surprisingly and unexpectedly achieved) according to Applicant's rejected claims. Applicant notes that 0.02% NaCl (120 ppm) chloride content – is still well above that achieved (see Summary Table 1 noted above) with the much simpler process of Applicant's rejected claims not requiring pre-digestion or extensive re-crystallization as required by Peverali in a completely different solvent system.

Moreover, because Cannata does not disclose, teach or suggest the IPA, methanol and water solvent system recited in Applicant's rejected claims, the combination of Peverali with Cannata does not and could not have arrived at Applicant's claimed invention.

Even further, there is no motivation to combine Peverali with Cannata because Peverali is directed to an ion-exchange free process whereas Cannata is not (as noted below). In particular, Peverali states in relevant part:

> DISCLOSURE OF THE INVENTION
>
> * * *

---

[1] Because 0.01% NaCl is about 60 ppm chloride content, the 0.06% NaCl of Peverali (Example 6) equates to a chloride content of about 364 ppm.

> Said process mainly uses water and small amounts of organic solvents; furthermore, neither ion exchange resins nor the specific industrial apparatuses involved are required. [(Peverali at col. 1, lines 52-55; emphasis added.)]

In direct contrast, the Cannata process is directed to an ion-exchange process as noted in relevant part below:

> [0001] The present invention relates to a process for the preparation of gabapentin and, more particularly, it relates to a process for the purification of gabapentin hydrochloride and for its conversion into gabapentin by treatment with a strong cationic ion exchange resin. [(Cannata at page 1, paragraph 0001, lines 1-5 thereof; emphasis added.)]

Without question, while Peverali is directed to an ion-exchange free process, Cannata (in direct contrast) is directed to an ion-exchange process. Accordingly, one of ordinary skill in the art would not have been motivated to combine references directed to such dis-similar and contradictory processes – one that is ion-exchange free and one that expressly relies on expensive ion-exchange – to then arrive at Applicant's claimed invention, which too "does not involve the costly ion-exchange conversion of gabapentin hydrochloride, making [Applicant's] process simpl[er] and [more] economical." The latter quote is taken from Applicant's specification originally filed at page 10, lines 4-7. (Emphasis added.)

Furthermore, in the chemical arts, it is not a matter of routine optimization to simply switch or change solvent systems and expect results amenable to optimization to achieve the low chloride and/or low lactam contents as surprisingly and unexpectedly achieved by Applicant. While the broad assertion that optimization is all that Applicant has achieved with his IPA/methanol/water solvent system has been made, such broad generic assertion does not take into account whether optimization is even possible (in the first place) to achieve the low chloride content and/or the low lactam content that Applicant has surprisingly and unexpectedly achieved (e.g., to 100 ppm or less chloride and/or low lactam content – see Summary Table 1 provided above).

There is no adequate predictability to disclose, teach or suggest that when changing from one solvent system to another, such change will not run up against insurmountable barriers that are unacceptable – such as not being able to achieve a low chloride and/or a low lactam content as Applicant has (surprisingly and unexpectedly) achieved.

For at least the foregoing reasons, Applicant respectfully submits that the claims 1-9 (as amended for improved clarity) are non-obvious and patentable under 35 USC § 103(a) over the combination of Peverali in view of Cannata.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-9 under 35 USC § 103(a) over Peverali in view of Cannata.

New Claims 13-20

Applicant also respectfully submits that new claims 13-20 are also patentable over the references of record. Thus, Applicant respectfully requests a written indication of the same.

CONCLUSION

There being no further outstanding objections or rejections, it is respectfully submitted that the application is in condition for allowance. An early action to that effect is courteously solicited.

Finally, if there are any outstanding matters remaining that may be resolved, the Examiner is earnestly requested to telephone the undersigned to promptly resolve these matters to a favorable conclusion.

If there are any additional fees associated with filing of this Amendment, please charge the same to our Deposit Account No. 19-3935, as needed.

Respectfully submitted,

STAAS & HALSEY LLP

Date: October 15, 2007

By: _____

Ajay Pathak
Registration No. 38,266

1201 New York Avenue, N.W., 7th Floor
Washington, D.C. 20005
Telephone: (202) 434-1500
Facsimile: (202) 434-1501

Attachments:
Fee Transmittal
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